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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,207	08/29/2003	Manuel J. Villa	99-006-Div	7626

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EXAMINER	
KATCHEVES, KONSTANTINA T	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/651,207	VILLA ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/9/04; 8/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 are pending in the present application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hinchliffe et

al. (U. S. Patent 5,637,504), in view of Hoffman et al. (US Patent 5,844,089), Buxton (US Patent 5,646,037) and Henry et al. (US Patent 5,529,912).

Hinchliffe et al. teach that yeast can produce commercially important polypeptides (column 3, line 59), and that the recombinant genes present in yeast should, so far as possible, be restricted to the gene of interest and adjacent yeast regulatory genes and that it is undesirable to have any extraneous DNA sequences such as bacterial plasmid sequences, which could have deleterious effects on the technological behaviour of the yeast (column 4, lines 22-35 and column 5, lines 25-44). Hinchliffe et al. teach a yeast plasmid, especially for Saccharomyces cerevisiae (column 1, lines 8-9), which comprises a selection gene marker which can be a gene such as LEU2, URA3, or TRP1 that complements a host auxotrophy (column 1, lines 45-52), a 2 μm origin of replication (see for example Abstract), and a gene of interest which can be homologous or heterologous to yeast (column 5 lines 45-55). This plasmid, upon transformation into yeast, undergoes FLP-mediated recombination to delete any bacterial DNA, and since the selection genes for laboratory yeast (such as S. cerevisiae) are genes that complement auxotrophies, any drug-resistance genes would have been for bacterial selection and thus deleted. The resulting yeast plasmid anticipates the instant claims, since the instant claims, as written, refer to plasmids with yeast origins of replication as "integration" plasmids, and the claims encompass plasmids in which the selection and targeting marker are the same gene.

Hoffman et al. teach co-expression in diploid yeast of two genes of interest from separate plasmids bearing 2-micron origins of replication. The genes of interest are alpha-globin and beta-globin. Plasmids for each gene of interest were constructed; these contain multiple yeast gene markers, such as *LEU2d* (a version of *LEU2*) and *TRP1*, or *LEU2d* and *URA3* (see for

example Fig. 22a-b). While neither of the two markers on a plasmid is used for targeting (integration), this limitation in Applicants' claims is merely a recitation of intended use, and the structure of the markers on Hoffman et al.'s plasmids could function in this way, and thus the recitation of intended use for either marker does not confer patentability (see above regarding recitations of intended use). Further, Hoffman et al. teach various haploid strains of *S. cerevisiae* of potential use for transformation of the expression vectors, including strains with various different auxotrophies, different protease gene mutations, different mating types, and so forth (see the table in column 27). Hoffman et al. teach transformation of the plasmids into haploid strains of different mating type, and then mating the strains to form a diploid that contains two plasmids, one expressing alpha-globin and the other expressing beta-globin. The results of expressing the two genes in one yeast were very favorable. See column 79, lines 14-67. Hoffman et al. do not teach plasmids without drug resistance genes.

Buxton teaches that it is desirable to express foreign genes in yeast with vectors that avoid the use of bacterial DNA (see for example, col. 2 lines 49-60 and col. 3 lines 44- 62) in order to improve stability. Buxton teaches plasmids and two types of ways to make them; one is similar to that of Hinchliffe. The other way of making a plasmid without bacterial DNA, as taught by Buxton, is preparation of the vector "directly, i.e., the final vector is constructed by ligating suitable DNA fragments, transformation of a suitable host and isolating it from the transformed host ... Preferred hosts are eukaryotic hosts, most preferentially yeast cells, because a symmetric vector of the invention does preferentially not contain bacterial DNA sequences." See column 5, lines 50-60. Thus, these vectors have no bacterial DNA even before transformation into yeast, as any non-yeast DNA would have been excised extracellularly.

Buxton further teaches examples using the yeast *S. cerevisiae*; in the Examples, the selectable marker genes are genes that complement auxotrophies, such as URA3, LEU2 (see, for example, columns 15-17). Since Buxton teaches avoidance of bacterial DNA, and since all of the markers taught for S. cerevisiae are genes that complement auxotrophies, inherent in Buxton is the teaching of plasmids for the yeast *S. cerevisiae* that do not contain drug-resistance markers, as there is no need for a drug resistance marker in *S. cerevisiae*. While Buxton's plasmids are not integration plasmids in the usual sense of the word, because they have yeast origins of replication, Applicants' claims, as currently worded, also encompass plasmids with yeast origins of replication.

Henry et al. teach the value of yeast expressing multiple copies of *INO1* for making inositol and other compounds.

At the time of the invention of the instant application, the ordinary artisan would have been motivated to express genes of interest in yeast, such as *S. cerevisiae*, because of multiple teachings in the art that teach the value of this, such as the teachings of Hinchliffe et al., Hoffman et al., and Buxton. The ordinary artisan would have been motivated to use plasmids that did not contain bacterial DNA, as taught by Hinchliffe et al. and Buxton, and for S. cerevisiae, the ordinary artisan would have been motivated to use as markers genes that complement auxotrophies, such as *URA3*, *LEU2*, and *TRP1*, since many references in the art teach such types of markers for *S. cerevisiae*. One would not have been motivated to use drug resistance genes, since these are not taught as usual for *S. cerevisiae* markers, and with respect to bacterial drug-resistance genes, Hinchliffe et al. and Buxton both teach avoiding bacterial DNA. The ordinary artisan would have been motivated to use vectors such as those of Hoffman et al.,

which contain several yeast markers, such as *LEU2* plus *URA*3 or *LEU2* plus *TRP1*, because Hoffman et al. teach these. Further, one would have been motivated to construct a suite of plasmids without bacterial DNA, such as by ligating fragments in vitro as taught by Buxton, because Hoffman et al. teaches the desirability of different strains of *S. cerevisiae* for transformation. That is, one would have wanted a suite of plasmids with the same gene of interest to have been able to transform yeast of different mating types, and the available yeast of different mating types may have different auxotrophies requiring different plasmid markers. One would also have been motivated to express different genes from different plasmids in the same strain; and as such would have need a suite of plasmids comprising different genes of interest (such as alpha globin and beta-globin). One would have been motivated to modify the teachings of Hoffman et al. to construct plasmids that did contain markers such as *URA3, LEU2*, and *TRP1* but that did not contain any bacterial DNA (including drug-resistance genes), for commercial production of the important genes of interest of Hoffman et al. (alpha and beta globin).

Moreover, one of ordinary skill in the art would have been motivated to construct plasmids without bacterial DNA for expression of genes of interest in yeast as taught by Hinchliffe et al. and Buxton, discussed above. Since Henry et al. teach *INO1* as a useful gene of interest, it would have been obvious to either integrate multiple copies of it, as taught by Henry et al., or to express multiple copies from, for example, a yeast 2 micron plasmid without any bacterial DNA (and without drug resistance markers, but instead only yeast selectable markers such as the *LEU2d* and *URA3* markers taught by Hoffman et al.). Therefore, the yeast strains claimed would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER